



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of ROBERTS ET AL.	Filed: November 17, 2003
Application No: 10/714,447	Attorney Docket No.: A1479-3P US
Art Unit: 1624	Examiner: Emily Bernhardt
Title: Novel Compounds with Analgesic Effects	

MAIL STOP APPEAL BRIEF-PATENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF PURSUANT TO 37 CFR 41.37

(1) REAL PARTY IN INTEREST

The real party in interest in this appeal is AstraZeneca Canada Inc. having a principal place of business at 1004 Middlegate road, Mississauga, Ontario L4Y 1M4, Canada.

AstraZeneca Canada Inc. is the assignee and owner of the entire interest in the above identified application by virtue of a series of assignments recorded in the United States Patent and Trademark Office on 1) April 24, 1997 at Reel/Frame 9531/0722, 2) September 24, 1998 at Reel/Frame 9232/0471, and 3) October 12, 2000 at Reel/Frame 011217/0591.

(2) RELATED APPEALS AND INTERFERENCES

The undersigned knows of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) STATUS OF THE CLAIMS

Claim 19 stands rejected and is the subject of this appeal.

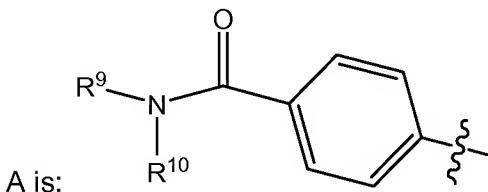
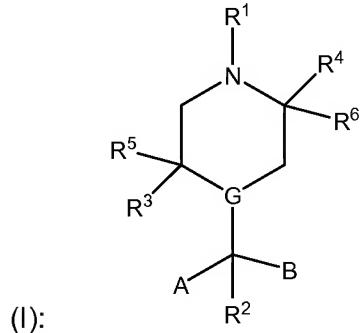
Claims 1-18 have been canceled.

(4) STATUS OF AMENDMENTS FILED SUBSEQUENT TO THE FINAL REJECTION

There have been no amendments filed subsequent to the Final rejection mailed February 16, 2006.

(5) SUMMARY OF THE CLAIMED SUBJECT MATTER

The claimed subject matter that forms the basis of this appeal is directed to piperazinyl compounds useful for binding to delta opioid receptors and treating pain represented by formula



wherein the phenyl ring of the A group is optionally substituted by one or two substituents independently selected from the group consisting of CH₃, CF₃ and halogen; R¹ is selected from the group consisting of: H; a branched or straight C₁–C₆ alkyl; –CO(C₁–C₆ alkyl); and (C₁–C₆ alkyl)-B' wherein B' is a C₆, C₉ or C₁₀ aryl or a 5 or 6 membered heteroaryl having a heteroatom selected from any of S, N and O and wherein the C₆, C₉ or C₁₀ aryl and the 5 or 6 membered heteroaryl are optionally substituted with 1 or 2 substituents selected from CH₃ or halogen;

R² is selected from the group consisting of H and CH₃;

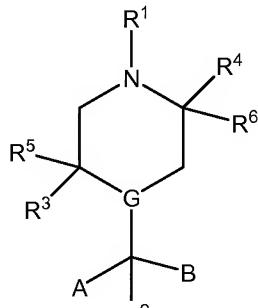
R⁹, and R¹⁰, are selected from the group consisting of H, a branched or straight C₁–C₆ alkyl and a C₂–C₆ alkenyl;

B is an C₆, C₉ or C₁₀ aromatic; or a C₆, C₉ or C₁₀ hydroaromatic; each being optionally substituted by 1 or 2 substituents independently selected from CH₃, CF₃, halogen, (CH₂)_pCONR⁷R⁸, (CH₂)_pNR⁷R⁸, (CH₂)_pCOR⁷, (CH₂)_pCO₂R⁷, OR⁷, (CH₂)_pSOR⁷, (CH₂)_pSO₂R⁷ and (CH₂)_pSO₂NR⁷R⁸;

wherein p is 0, 1, or 2, and wherein R⁷ and R⁸ are selected from: H; a branched or straight C₁–C₆ alkyl; or –CO(C₁–C₆ alkyl); and

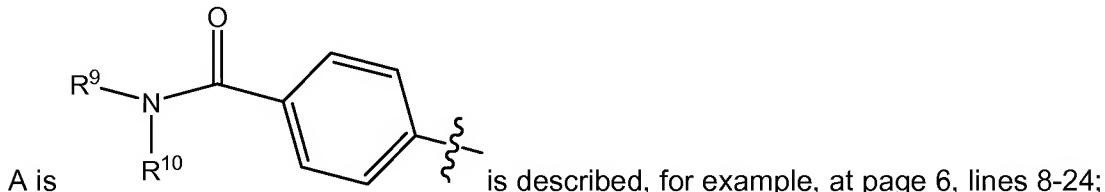
R³, R⁴, R⁵, and R⁶ are each H;

as well as pharmaceutically acceptable salts, hydrates, isoforms and isomers, other than positional isomers, thereof.



Formula (I) is described, for example, at page 3, lines 1-5.

G is N (nitrogen) is described, for example, at page 9, line 5 and Examples 1-48 and 50-56.



A is is described, for example, at page 6, lines 8-24;

page 9, lines 6-10; and Examples 21-39, 42, and 49-51.

The R¹ that is selected from the group consisting of H; a branched or straight C₁–C₆ alkyl; –CO(C₁–C₆ alkyl); and (C₁–C₆ alkyl)-B' is described, for example, at page 4, lines 13-20; page 7, lines 1-4; page 9, line 18; and Examples 1, 4, 7, 12, 13, 18, 21, 23, 25, 27-31, 34, 35, 37, 38, 40, 42, 43, 45-50, and 51-56.

The B' that is a C₆, C₉ or C₁₀ aryl or a 5 or 6 membered heteroaryl having a heteroatom selected from any of S, N and O and wherein the C₆, C₉ or C₁₀ aryl and the 5 or 6-membered heteroaryl are optionally substituted with 1 or 2 substituents selected from CH₃ or halogen is described, for example, at page 4, line 14 and page 5, lines 5-10; page 7, lines 2 and 11-20; and Examples 52-56.

The R² that is selected from the group consisting of H and CH₃ is described, for example, at page 4, line 24; page 7, line 6; page 9, line 20; and Examples 1-56.

The R⁹ and R¹⁰ that are selected from the group consisting of H, a branched or straight C₁–C₆ alkyl and a C₂–C₆ alkenyl are described, for example, at page 5, line 1

and page 4, lines 13-20; page 7, lines 1-4 and 8-9; page 9, line 16; and Examples 21-39, 42, and 49-51.

The B that is a C₆, C₉ or C₁₀ aromatic; or a C₆, C₉ or C₁₀ hydroaromatic; each being optionally substituted by 1 or 2 substituents independently selected from CH₃, CF₃, halogen, (CH₂)_pCONR⁷R⁸, (CH₂)_pNR⁷R⁸, (CH₂)_pCOR⁷, (CH₂)_pCO₂R⁷, OR⁷, (CH₂)_pSOR⁷, (CH₂)_pSO₂R⁷ and (CH₂)_pSO₂NR⁷R⁸ is described, for example, at page 5, lines 5-10; page 7, lines 11-20; page 10, lines 1-10; and Examples 1-56.

The p that is 0, 1, or 2 is described, for example, at page 5, line 12; page 10, line 19; and Examples 1-56.

The R⁷ and R⁸ that are selected from: H; a branched or straight C₁-C₆ alkyl; or –CO(C₁-C₆ alkyl) are described, for example, at page 4, lines 13-22; page 7, lines 1-4; page 10, line 12 and page 9, line 18; and Examples 1-20, 31-34, 38-41, and 50-51.

The R³, R⁴, R⁵, and R⁶ that are each H are described, for example, at 21-30, 35-36, and 42-56.

The pharmaceutically acceptable salts of Formula (I) are described, for example, at page 6, lines 1-2 and page 85, lines 13-24.

The hydrates of Formula (I) are described, for example, at page 6, lines 1-2.

The isoforms of Formula (I) are described, for example, at page 6, lines 1-2 and page 11, lines 16-17.

The isomers, other than positional isomers, of Formula (I) are described, for example, at page 6, lines 1-2 and page 11, lines 12-14.

(6) GROUNDS OF REJECTION PRESENTED FOR REVIEW

a. 35 U.S.C. § 103(a)

Claim 19 stands rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Calderon et al. and Bilsky et al. references in view of Chang et al. (PCT Publication WO93/15062 or U.S. Pat. No. 5,658,908, applied as of its § 102(e) date).

(7) ARGUMENTS

The Examiner has failed to establish a prima facie case of obviousness because there is no motivation or suggestion to modify and/or combine the reference's on which the Examiner relies.

The full citations for the Calderon et al. and Bilsky et al. references are set forth in Appendix D submitted herewith. The Calderon et al. and Bilsky et al. references were cited as C1, C2, C4, and C5 in the Information Disclosure Statement submitted by Applicants on November 17, 2003.

In the March 22, 2005 final office action, the Examiner asserted on page 2 that the presently claimed compounds of formula (I) are obvious variants over Calderon et al. and Bilsky et al. in view of Chang et al. because Chang et al. supposedly teaches that the hydrogen and methyl on the piperazine ring carbons of Chang et al. are interchangeable in similar compounds having the same use as described in Chang et al. The Examiner supported this notion of interchangeability by pointing to disclosures in Chang et al. that allegedly indicate R3-R5 can be either hydrogen or methyl; R6 can be hydrogen, alkyl, cycloalkyl, or arylalkyl; and that the “instant compounds are within the preferred embodiments taught in col. 6.” See, Final Office Action dated March 22, 2005, at pages 2-3. The Examiner concluded that the interchangeability allegedly taught by Chang et al. was akin to an “equivalency teaching” and therefore “it would have been obvious to one skilled in the art at the time the instant invention was made to replace the aforementioned groups in ...[Bilsky et al. and Calderon et al.] with those present herein at instant R1 and R3-R6 and in so doing obtain additional compounds for treating pain” See, Final Office Action dated March 22, 2005, at page 3.

The Calderon et al. and Bilsky et al. references only disclose compounds having dimethyl groups substituted on the carbons of the central piperazine ring. In fact, under the heading “Chemistry” at page 696 in the Calderon et al. reference identified as C5 in Applicants’ IDS, Calderon et al. expressly emphasizes the importance of using a dimethyl substituted intermediate, which is chiral due to the dimethyl substitution, to synthesize the dimethyl substituted final product. But for the dimethyl group on the piperazine ring, the intermediate used by Calderon et al. would have been achiral and the resulting products would not have been readily separable and optically pure.

In contrast, Claim 19 of Applicants’ claimed invention is directed to compounds containing an unsubstituted central piperazine ring, wherein Claim 19 defines the R³, R⁴, R⁵, and R⁶ substituent groups of formula (I) so as to limit such groups to hydrogen. The Examiner acknowledges this difference on page 2 of the Final Office Action, but proposes that Calderon et al. and Bilsky et al. be combined with Chang et al. to eliminate the dimethyl substituents on the central piperazine of the Bilsky et al. and Calderon et al. references.

Applicants, however, respectfully disagree with the Examiner’s proposition because

Chang et al. does not teach that hydrogen and methyl behave equivalently and are therefore readily interchangeable. Indeed, at the time the present application was filed, a person of ordinary skill in the art upon viewing Chang et al. as a whole would not have been motivated to modify the compounds disclosed in Calderon et al. and/or Bilsky et al. so as to arrive at the presently claimed compounds. In fact, it would have been reasonable for a person of ordinary skill in the art when viewing Calderon et al.'s and Bilsky et al.'s dimethylated piperazinyl compounds in light of Chang et al.'s own preference for methylated piperazinyl compounds to have understood Chang et al.'s express statements to mean that methyl and hydrogen did not behave equivalently and—contrary to the Examiner's position—were not interchangeable. Chang et al. stated during prosecution of U.S. Pat. No. 5,658,908 (hereinafter "the '908 patent") that methyl and hydrogen did not behave equivalently and Bilsky et al.'s and Calderon et al.'s preference for dimethylated piperazinyl compounds seemingly validated Chang et al.'s nonequivalency statement. As a result, in contrast to the Examiner's assertions, the person of ordinary skill in the art upon viewing Chang et al. as a whole would have been motivated to retain the methyl groups on the piperazinyl of the Bilsky et al and/or Calderon et al. compounds.

As the Federal Circuit explained in the recently decided Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd. case, a prima facie case of obviousness regarding a structurally similar claimed and prior art compound is only made out when the prior art gives reason or motivation to make the claimed compound. No. 06-1329, 2007 U.S. App. LEXIS 15349, at *11, 83 U.S.P.Q.2D 1169, 1174 (Fed. Cir. June 28, 2007). The court further explained that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." Id. at *11, 83 U.S.P.Q.2D at 1174. The court noted that a prima facie case of obviousness can be based on structural similarity where the structural relationship may provide the requisite motivation or suggestion to modify the known compound to arrive at the claimed compound. Id. at *11-12, 83 U.S.P.Q.2D at 1174. The court noted that while a "known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties'", it still remained necessary "in cases involving new chemical compounds ... to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie case of obviousness of a new claimed compound." Id. at *12, 83 U.S.P.Q.2D at 1174. The Federal Circuit went on to confirm that the test for establishing a prima facie case of obviousness of a structurally similar claimed

and prior art compound as set forth hereinabove is consistent with the legal principles set forth in the recently decided Supreme Court case, KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). Id. at *12, 83 U.S.P.Q.2D at 1174.

In the case at hand, Chang et al. expressly stated during the prosecution of the '908 patent that methyl and hydrogen did not behave equivalently and therefore were not readily interchangeable. More specifically, Chang et al. stated in relevant part in reliance on a 132 declaration as follows:

Specifically, these tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II, had no substituents on carbon atoms of the piperazine ring. The other compound of the pair was the same as the first, except that it had two methyl groups on carbon atoms of the piperazine ring. The test results, *comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity.* (Emphasis added).

(See page 60 of the February 9, 1996 response attached hereto as Appendix B and made of record in Applicants' November 30, 2005 response.) As the scope and content of prior art includes the prosecution history associated with the prior art, Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd., No. 06-1329, 2007 U.S. App. LEXIS 15349, at *32-34; 83 U.S.P.Q.2D 1169, 1179 (Fed. Cir. June 28, 2007), and Chang et al.'s own words clearly indicate Chang et al. did not believe methyl and hydrogen behaved equivalently and were therefore readily interchangeable, a person of ordinary skill in the art upon viewing Chang et al. as a whole would not have been motivated to modify the compounds disclosed in Bilsky et al. and/or Calderon et al. so as to arrive at the presently claimed compounds.

This conclusion is further buttressed by Chang et al.'s repeated statements throughout the specification of the '908 patent that the preferred compounds that exhibit delta-opioid and/or mu-opioid agonist activity have methyl substituted on the piperazinyl ring at at least one of the R³, R⁴ and R⁵ positions. (See, col. 5, lines 36-38; col. 6, line 20 to column 7, line 17; col. 18, line 65 to col. 19, line 54; col 19, line 66 to col. 20, line 50; col. 20, line 62 to col. 22, line 16; col. 23, lines 3-18; col. 24, line 10 to col. 25, line 8; and col. 112, lines 25-29 of the '908 patent). And yet further buttressed by the fact that the Example 1-50, 53-76, and 78-91 compounds disclosed by Chang et al. are substituted on the piperazinyl ring by 2 or more methyl groups. Specifically, Examples 1-11, 14-33, 35-38, and 40-91 contain a dimethyl substituted piperazinyl ring, while Examples 12, 13, 34, and 39 contain a trimethyl substituted piperazinyl ring. Please

note, Examples 51, 52, and 77 contain piperidinyl—not piperazinyl—rings. And even yet further buttressed by the fact that the “particularly preferred compounds” identified by Chang et al. at col. 15, lines 17-22 of the ‘908 patent all have a dimethyl substituted piperazinyl ring.

For all of the reasons set forth hereinabove, it would have been reasonable for a person of ordinary skill in the art when viewing Calderon et al.’s and Bilsky et al.’s dimethylated piperazinyl compounds in light of Chang et al.’s own preference for methylated piperazinyl compounds to have understood Chang et al.’s express statements to mean that methyl and hydrogen did not behave equivalently and—contrary to the Examiner’s position—were not interchangeable. Chang et al. stated that methyl and hydrogen did not behave equivalently and Bilsky et al.’s and Calderon et al.’s preference for dimethylated piperazinyl compounds seemingly validated Chang et al.’s nonequivalency statement. As a result, Applicants respectfully assert that Calderon et al., Bilsky et al. and Chang et al. all lacked the requisite suggestion and/or motivation to eliminate the methyl groups from the carbons of the central piperazinyl of the Calderon et al. and/or Bilsky et al. compounds so as to arrive at Applicants’ claimed invention. Accordingly, claim 19 is not obvious over Bilsky et al. and Calderon et al. in view of Chang et al.

In sum, a person of ordinary skill in the art upon reading Bilsky et al., Calderon et al., and/or Chang et al. as a whole would not have been motivated at the time the present application was filed to replace the methyl groups of the dimethylated compounds of Calderon et al. or Bilsky et al. with the hydrogens of Chang et al. because Chang et al.’s own words indicated methyl and hydrogen do not behave equivalently and are therefore not readily interchangeable. Accordingly, Applicants respectfully submit that the Examiner made clear errors and/or omitted one or more essential elements needed to establish a *prima facie* case of obviousness, and therefore respectfully request that the Examiner’s rejection of claim 19 as obvious over Calderon et al. and Bilsky et al. in view of Chang et al. be reversed.

Respectfully submitted,

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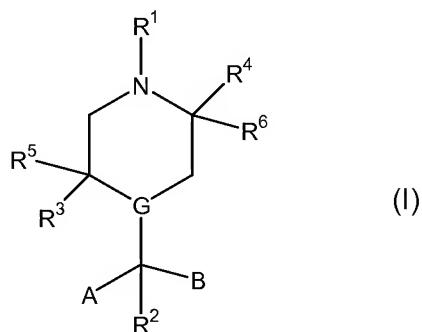
/Jacqueline M. Cohen/

Name: Jacqueline M. Cohen
Dated: August 13, 2007
Reg. No: 51,574

**APPENDIX A
COPY OF CLAIM INVOLVED IN APPEAL**

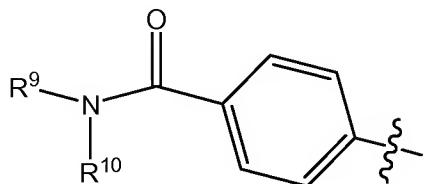
Claims 1-18. (Cancelled).

19. A compound of formula (I)



wherein G is a nitrogen atom;

A is:



wherein the phenyl ring of the A group is optionally substituted by one or two substituents independently selected from the group consisting of CH₃, CF₃ and halogen;

R¹ is selected from the group consisting of: H; a branched or straight C₁–C₆ alkyl; –CO(C₁–C₆ alkyl); and (C₁–C₆ alkyl)-B' wherein B' is a C₆, C₉ or C₁₀ aryl or a 5 or 6 membered heteroaryl having a heteroatom selected from any of S, N and O and wherein the C₆, C₉ or C₁₀ aryl and the 5 or 6 membered heteroaryl are optionally substituted with 1 or 2 substituents selected from CH₃ or halogen;

R² is selected from the group consisting of H and CH₃;

R⁹, and R¹⁰, are selected from the group consisting of H, a branched or straight C₁–C₆ alkyl and a C₂–C₆ alkenyl;

B is an C₆, C₉ or C₁₀ aromatic; or a C₆, C₉ or C₁₀ hydroaromatic; each being optionally substituted by 1 or 2 substituents independently selected from CH₃, CF₃, halogen, (CH₂)_pCONR⁷R⁸, (CH₂)_pNR⁷R⁸, (CH₂)_pCOR⁷, (CH₂)_pCO₂R⁷, OR⁷, (CH₂)_pSOR⁷, (CH₂)_pSO₂R⁷ and (CH₂)_pSO₂NR⁷R⁸;

wherein p is 0, 1, or 2, and wherein R⁷ and R⁸ are selected from: H; a branched or straight C₁–C₆ alkyl; or –CO(C₁–C₆ alkyl);

R³, R⁴, R⁵, and R⁶ are each H;

as well as pharmaceutically acceptable salts, hydrates, isoforms and isomers, other than positional isomers, thereof.

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APPENDIX B

EVIDENCE APPENDIX

Please see comments made in Chang et al.'s February 9, 1996 response attached hereto.

These pages were made of record in Applicants' November 30, 2005 response.



Appendix I

Patent Application
3022-107

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kwen-Jen CHANG, et al.

Group Art Unit: 1202

Application No. 08/284,445

Examiner: E. Bernhardt

Date Filed: August 3, 1994

For: **"OPIOID DIARYLMETHYLPIPERAZINES AND PIPERIDINES"**

EXPRESS MAIL CERTIFICATE

It hereby is certified by the person identified below that this paper is being mailed by such person to the Commissioner of Patents and Trademarks on the date specified, in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231, and Express Mailed under the provisions of 37 CFR 1.10.

Mary B. Caruso
Signature

MARY B. CARUSO
Name of Person Mailing This Paper

FEBRUARY 9, 1996
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AMENDMENT RESPONDING TO AUGUST 9, 1995 OFFICE ACTION IN U.S. PATENT APPLICATION NO. 08/284,445

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the 9 August 1995 Office Action in the above-identified application,
please amend the application, as follows:

In the Claims

Amend the claims as follows:

B

Appendix I - Continued

Patent Application
3022-107

The Examiner has requested the month of publication for references BD-BH, which are as follows. BD: November, 1993; BE: October, 1993; BF: November, 1993; BG: November, 1993; BH: November, 1993.

Claims 1-8, 12-14, 38-40 and 44 were rejected in the 9 August 1995 Office Action as being drawn to improper Markush group(s) on the basis that the variables G, R⁹ and R¹⁰ embrace more than one invention as discussed in the restriction requirement.

In the restriction requirement dated April 5, 1995, the Examiner sought to limit claim 1 to G=N and exclude R⁹ and R¹⁰ from being C₃ and higher. Applicants respectfully disagree with this suggestion, particularly since the claims have already been examined on the merits. Furthermore, according to M.P.E.P. Section 803,

*Cand G=10
reexam
to C₃
markush
of merits
M.P.E.P.*

"[i]f the search and examination of an entire application can be made without serious burden, the examiner **must** examine it on the merits, even though it includes claims to distinct or independent inventions."

Thus, since examination on the merits has already occurred, it is clear that the Markush groups of the claims are in proper form according to the M.P.E.P.

For the foregoing reasons, the Section 112 rejections have been overcome, as described in the above discussion, and through the foregoing amendments, which serve to clarify claims 1, 5, 7, 12, 14-17, 38 and 44.

Arguments for Patentability

Appendix I - Continued

Patent Application
3022-107

As discussed above, references AM, AS-AU and BD-BH do not qualify as prior art.

Claims 1, 3, 14-17 and 38-40 were rejected in the 9 August 1995 Office Action under 35 U.S.C. Section 102(b) over references AW and AY. Furthermore, claims 20, 21 and 24 were rejected in the 9 August 1995 Office Action under 35 U.S.C. Section 103 over references AW and AY.

AW and AY are directed to a calcium antagonist, KB-2796, which is I-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride. Related compounds A, B, C, Flunarazine and Cinnarizine are also discussed. (See the structural configurations in AW, Figure 1 and AY, Table 1.) None of the compounds discussed in AW or AY teach or suggest the compounds of the present invention.

Instead, the present invention, as claimed, is related to opioid diarylmethylpiperazines and piperidines. The claims of the present invention, as amended, are directed to diarylmethylpiperazines and piperidines having a particular type of substituent attached to at least one of the carbon atoms in the piperazine ring. For example, according to claim 1, as amended, the substituents on the piperazine are as follows:

"R³, R⁴ and R⁵ may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R³, R⁴ or R⁵ is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R³, R⁴ and R⁵ together may form a bridge of 1 to 3 carbon atoms."

Appendix I - Continued

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3022-107

In contrast, AW and AY do not teach or suggest such compounds having a substituent attached to at least one of the carbon atoms in the piperazine ring.

132?

According to the enclosed Declaration under 37 C.F.R. 1.131 by Dr. Robert McNutt, comparisons have been made between compounds that have a substituent attached to at least one of the carbon atoms in the piperazine ring and those that do not, using the assay procedures set out in Example 92 on pages 156-157 of the specification.

Specifically, these tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II, had no substituents on carbon atoms of the piperazine ring. The other compound of the pair was the same as the first, except that it had two methyl groups on carbon atoms of the piperazine ring. The test results, comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity.

The compounds tested were as follows, wherein Compounds 1-4 have no substituents on carbon atoms of the piperazine ring, and Compounds 1a-4a have two methyl groups on carbon atoms of the piperazine ring:

Compound 1: (+)-3-($\ddot{\tau}$ -(4-Allyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 1a: (+)-3-(($\ddot{\tau}$ R*)- $\ddot{\tau}$ -((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 2: (+)-3-($\ddot{\tau}$ -(4-Allyl-1-piperazinyl)-4-bromobenzyl)phenol;

Appendix I - Continued

Patent Application
3022-107

Compound 2a: (+)-3-(($\ddot{\tau}$ R*)- $\ddot{\tau}$ -((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 3: (+)-3-($\ddot{\tau}$ -(4-Allyl-1-piperazinyl)benzyl)phenol;

Compound 3a: (+)-3-(($\ddot{\tau}$ R*)- $\ddot{\tau}$ -((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

Compound 4: (+)-3-($\ddot{\tau}$ -(4-Methyl-1-piperazinyl)benzyl)phenol; and

Compound 4a: (+)-3-(($\ddot{\tau}$ R*)- $\ddot{\tau}$ -((2R*,5S*)-2,4,5-Trimethyl-1-piperazinyl)benzyl)phenol.

The compounds having methyl groups on the piperazine ring can be found in the present specification as follows. Compound 1a can be found, for example, on page 12, number 1. Compound 2a can be found, for example, on page 14, number 40. Compound 3a can be found, for example, on page 15, number 47. Compound 4a can be found, for example, on page 21, number 136.

The test results for Compounds 1-4 and Compound 1a-4a using assays described in Example 92 on pages 156-157 of the specification are as follows:

Compound	Mu Receptor IC50 (nM)	Mouse Vas Deferens ED50 (nM)	Delta Receptor IC50 (nM)
Compound 1	3500	2000	50
Compound 1a	90	40	15
Compound 2	2000	*	60
Compound 2a	200	100	80
Compound 3	200	nd	60
Compound 3a	25	78	1.3
Compound 4	700	nd	140
Compound 4a	1.6	46	38

Appendix I - Continued

Patent Application
3022-107

nd = not determined

* Test results showed that Compound 2 has antagonist activity rather than agonist activity in the mouse vas deferens assay

According to Dr. McNutt's Declaration, the test results show that substituted Compound 1a has fifty times more potency than unsubstituted Compound 1 according to the Mouse Vas Deferens ED50, more than thirty times more potency according to the Mu Receptor IC50, and more than three times more potency according to the Delta Receptor IC50. Substituted Compound 2a has ten times more potency than Compound 2 according to the Mu Receptor IC50. Substituted Compound 3a has more than 45 times more potency than unsubstituted Compound 3 according to the Delta Receptor IC50 and 8 times more potency according to the Mu Receptor IC50. Compound 4a has more than four hundred times more potency than unsubstituted Compound 4 according to the Mu Receptor IC50 and more than three times more potency according to the Delta Receptor IC50.

Thus, the test results comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity according to test results of assays described in Example 92 on pages 156-157 of the specification. This general trend was an unexpected result of the addition of a substituent on the piperazine ring, which is not taught or suggested by the calcium antagonists disclosed in references AW or AY, taken alone or in combination.

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Thus, references AW and AY do not teach or suggest the compounds of the present invention, as claimed, which is directed to opioid diarylmethylpiperazines and piperidines in which there is a substituent attached to at least one of the carbon atoms in the piperazine ring.

Applicants note for the record that claims 4-8, 12, 13, 18, 19, 23, 25-28, 44, 64 and 65 have been found patentable over the prior art, particularly since AS-AU, BD-BH and AM do not qualify as prior art as discussed above.

For all of the foregoing reasons, claims 1, 3-8, 12-21, 23-28, 38-40, 44, 64 and 65, as amended, are fully patentably distinguished over the references cited and are in condition for allowance.

If any issues remain outstanding in connection with the allowance of this application, the Examiner is requested to contact the undersigned attorney, at (919) 990-9531 to discuss their resolution, so that this application can be passed to issue at an early date, consistent with the substantial advance in the art achieved by the invention claimed in this application.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kwen-Jen CHANG, et al.

Group Art Unit: 1202

Application No. 08/284,445

Examiner: E. Bernhardt

Date Filed: August 3, 1994

For: **"OPIOID DIARYLMETHYLPIPERAZINES AND PIPERIDINES"**

EXPRESS MAIL CERTIFICATE

It hereby is certified by the person identified below that this paper is being mailed by such person to the Commissioner of Patents and Trademarks on the date specified, in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231, and Express Mailed under the provisions of 37 CFR 1.10.

Mary B. Caruso
Signature

MARY B. CARUSO
Name of Person Mailing This Paper

FEBRUARY 9, 1996
Date of Mailing

FG561244191305
Express Mail Label Number

DECLARATION OF DR. ROBERT MCNUTT UNDER 37 C.F.R. Section 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Robert Walton McNutt, Jr., hereby declare and state the following:

1. I am a citizen of the United States of America, residing at 700 Morreene Road, Durham, NC 27705, and hold a Ph.D. in organic chemistry from Boston College, granted in 1977, and I have been employed by Burroughs Wellcome, now Glaxo Wellcome, since 1979 and continuing to date, currently holding the position of Research Scientist in such company.

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2. I am an inventor of subject matter described and claimed in United States Patent Application Serial No. 08/284,445 filed 03 August 1994 in the names of Kwen-Jen Chang, Grady Evan Boswell, Dulce Garrido Bubacz, Mark Allan Collins, Ann Otstot Davis, and Robert Walton McNutt, Jr. (and hereinafter referred to as the "Application").

3. I am aware that the United States Patent and Trademark Office has issued an Office Action dated 09 August 1995 in the Application, and that in such Office Action, among other rejections, claims 1, 3, 14-17 and 38-40 were rejected under 35 U.S.C. Section 102(b) as anticipated by references AW and AY, and claims 20, 21 and 24 were rejected as obvious in view of references AW and AY. References AW and AY are as follows:

AW Iwamoto et al., "Calcium Antagonism by KB-2796, a New Diphenylpiperazine Analogue, in Dog Vascular Smooth Muscle," *J. Pharm. Pharmacol.* 43, 535-539, 1991 ("Iwamoto I"); and

AY Iwamoto et al., "Effects of KB-2796, a New Calcium Antagonist, and Other Diphenylpiperazines on [3H]Nitrendipine Binding," *J. Pharmacol.*, 48, 241-247 (1988) ("Iwamoto II").

4. I have read and am familiar with the references identified in Paragraph 3 above.

5. The references identified in Paragraph 3 above disclose the following compounds:

"Compound A": 3-(4-chloro- α -(4-(3-methylbenzyl)piperazinyl)benzyl)phenol;

"Compound B": 1-(bis(4-methoxyphenyl)methyl)-4-(2,3,4-trimethoxybenzyl)piperazine;

"Compound C": 1-(bis(4-fluorophenyl)methyl)-4-(3-(2,3,4-trimethoxyphenyl)-2-propen-1-yl)piperazine;

KB-2796: 1-bis(4-fluorophenyl)methyl)-4-(2,3,4-trimethoxybenzyl)piperazine;

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Flumarizine: 1-(bis(4-fluorophenyl)methyl)-4-(3-phenyl-2-propen-1-yl)piperazine; and

Cinnarizine: 1-(diphenylmethyl)-4-(3-phenyl-2-propen-1-yl)piperazine.

6. None of the compounds disclosed in Iwamoto I or II, as identified in Paragraph 5 above, have any substituents attached to any of the carbon atoms in the piperazine ring.

7. I have collaborated on tests conducted on certain diphenylpiperazine compounds using the assay procedures set out in Example 92 on pages 156-157 of the specification of the Application. These tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II and identified in Paragraph 5 above, had no substituents on the carbon atoms of the piperazine ring. The other compound of the pair was the same as the first except that it had two methyl groups on the carbon atoms of the piperazine ring.

8. The compounds tested according to Paragraph 7 were as follows, wherein Compounds 1-4 have no substituents on the carbon atoms of the piperazine ring, and Compounds 1a-4a have two methyl groups on the carbon atoms of the piperazine ring:

Compound 1: (\pm)-3-(α -(4-Allyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 1a: (\pm)-3-((α R*)- α -((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 2: (\pm)-3-(α -(4-Allyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 2a: (\pm)-3-((α R*)- α -((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 3: (\pm)-3-(α -(4-Allyl-1-piperazinyl)benzyl)phenol;

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Compound 3a: (\pm)-3-((α R*)- α -((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

Compound 4: (\pm)-3-(α -(4-Methyl-1-piperazinyl)benzyl)phenol; and

Compound 4a: (\pm)-3-((α R*)- α -((2R*,5S*)-2,4,5-Trimethyl-1-piperazinyl)benzyl)phenol.

9. The test results for Compounds 1-4 and Compound 1a- 4a described in Paragraphs 7-8, using assays described in Example 92 on pages 156-157 of the specification of the Application, are as follows:

Compound	Mu Receptor IC50 (nM)	Mouse Vas Deferens ED50 (nM)	Delta Receptor IC50 (nM)
Compound 1	3500	2000	50
Compound 1a	90	40	15
Compound 2	2000	*	60
Compound 2a	200	100	80
Compound 3	200	nd	60
Compound 3a	25	78	1.3
Compound 4	700	nd	140
Compound 4a	1.6	46	38

nd = not determined

*Test results showed that Compound 2 has antagonistic activity rather than agonist activity in the mouse vas deferens assay

10. The test results listed in Paragraph 9 above show that substituted Compound 1a has fifty times more potency than unsubstituted Compound 1 according to the Mouse Vas Deferens ED50, more than thirty times more potency according to the Mu Receptor IC50, and more than three times more potency according to the Delta Receptor IC50. Substituted Compound 2a has ten times more potency than Compound 2 according to the Mu Receptor IC50. Substituted Compound 3a has more than 45 times more potency than unsubstituted Compound 3 according to the Delta Receptor IC50 and 8 times more potency according to the Mu Receptor IC50. Compound 4a has more than four hundred

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times more potency than unsubstituted Compound 4 according to the Mu Receptor IC50 and more than three times more potency according to the Delta Receptor IC50.

11. The test results in Paragraphs 9 and 10 above comparing compounds in which the piperazine ring is substituted with two methyl groups on the carbon atoms with those that do not have a substituent on any of the carbon atoms of the piperazine ring show a general trend in which the substituted compounds have significantly greater opioid activity according to test results of assays described in Example 92 on pages 156-157 of the specification of the Application.

All statements made herein of my own knowledge are true, and all statements made on inference and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.


Robert Walton McNutt, Jr.
Dr. Robert Walton McNutt, Jr.

Date: February 7, 1996

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**APPENDIX C
RELATED PROCEEDINGS APPENDIX**

None.

**APPENDIX D
LIST OF REFERENCES RELIED ON BY EXAMINER**

- 1) WO93/15062.
- 2) U.S. Pat. No. 5,658,908.
- 3) Bilsky, et al., "Characterization of Enantiomers of (\pm)BW373U86 and Related Compounds: Highly Selective Nonpeptidic Delta Opioid Agonists," *Reg. Peptides* 54:25-26(1994)—**Cited as C1 in Applicants' November 17, 2003 IDS.**
- 4) Bilsky, et al., "SNC 80, A Selective, Nonpeptidic and Systemically Active Opioid Delta Agonist," *J. Pharmacol. Exper. Therap.* 273:359-366 (1995)—**Cited as C2 in Applicants' November 17, 2003 IDS.**
- 5) Calderon, et al., "Probes for Narcotic Receptor Mediated Phenomena. 19. Synthesis of (+)-4-[(αR) - α -((2S,5R)-4-Allyl-2,5-Dimethyl-1-Piperazinyl)-3-Methoxybenzyl]-N,N-Diethylbenzamide (SNC 80): A Highly Selective, Nonpeptide Δ Opioid Receptor Agonist," *J. Med. Chem.* 37:2125-2128 (1994)—**Cited as C4 in Applicants' November 17, 2003 IDS.**
- 6) Calderon, et al., "Probes for Narcotic Receptor Mediated Phenomena. 23. Synthesis, Opioid Receptor Binding, and Bioassay of the Highly Selective δ Agonist (+)-4-[(αR) - α -((2S,5R)-4-Allyl-2,5-Dimethyl-1-Piperazinyl)-3-Methoxybenzyl]-N,N-Diethylbenzamide (SNC 80) and Related Novel Nonpeptide Δ Opioid Receptor Ligands," *J. Med. Chem.* 40:695-704 (1997)—**Cited as C5 in Applicants' November 17, 2003 IDS.**